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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/515,582	02/29/2000	Roland Buelow	A-63708-5/RFT/JJD	9803

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EXAMINER
LI, QIAN J

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/515,582	BUELOW ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-12,16-22 and 28-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-12,16-22 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 February 2000* is/are a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

The amendment and response filed on 4/9/03 has been entered and assigned as Paper # 15. Claims 1-3, 13-15, 26, and 27 have been canceled. Claims 4-7, 9-12, 16-18, 20-22 have been amended. Claims 28-31 are newly submitted. Claims 4-12, 16-22, and 28-31 are pending and under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The argument in paper #15 would be addressed to the extend that it reads on the current rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

ENABLEMENT REQUIREMENT

Claims 4-12, 16-22, and 28-31 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in paper#13, and following.

With regard to types of vectors used in the therapy and the means of delivering DNA into cells in vivo and ex vivo, applicants argue that long term expression is not required for this method and submitted numerous references as enablement support for broadly claimed methods in paper #15.

The argument and references have been fully considered but they are not persuasive to support the full scope of the claims for reasons of record and following.

The instantly claimed methods require a therapeutic effect, i.e. extending the survival of an organ explant, thus, sufficient numbers of cells have to be transfected. Thus, even though the long term expression may not be necessary, "ABILITY TO TARGET A GENE TO A SIGNIFICANT POPULATION OF CELLS AND EXPRESS IT AT ADEQUATE LEVELS as taught by *Deonarain* is required. This is also the essence of the teaching by Miller et al, who call for highly efficient delivery systems. The newly submitted references do not support the full scope of the claims because first, many of the references use direct injection and perfusion of the nucleic acids, such as Exhibits D, E, H, I, J, K, L, and M. Secondly, even with direct delivery, not all nucleic acids are sufficiently expressed. For example, *Qin et al* (Exhibit E) teach that 2 out of 3 types of plasmid vectors fail to be detectably expressed in vivo in myocytes wherein the vectors are delivered by direct injection; and only one of the four syngeneic hosts could express a retroviral vector in vivo (table 4). Thirdly, *Kuemmerle et al* (Exhibit C) teach locally and intravenously delivering plasmid vector to renal cells, and the expression could be detected after 6 months. However, they fails to teach whether sufficient numbers of cells in the target organ could be transfected at high enough level so that a therapeutic effect could be achieved. Fourthly, certain vectors such as the herpes vector have high cytotoxicity as illustrated in table 1 of Exhibit H, thus would not be suitable for preserving organ transplants. Fifthly, Exhibit F is a post-filing publication, thus could not be used as enablement support for the specification *at the time* the present application was filed.

with regard to in vivo gene targeting, applicants argue in paper #15 that applicants have reduced to practice in example 3 of the specification showing that intravenous administration of Ad-HO-I vector extends the survival of a transplant, even in the absence of specific targeting, and concluded that tissue or cell targeting is not necessary to achieve the desired results.

The argument has been fully considered but they are not persuasive. This is because it is a well known in the art that viral vectors possess tissue tropism. For adenoviral vector, intravenous injection would lead to high concentration of vectors in the liver because hepatocytes possess more high-affinity Coxsackie/adenovirus receptor for the cell entry of the adv. Example 3 reduced to practice aiming to pre-treating a liver graft. Therefore, even though the applicants may not intend to perform gene targeting, the adenoviral vector intrinsically target the vector to liver cells, and achieved desired effects. Moreover, liver is an exceptional organ that would collectively accept many substances that are destined to be eliminated by the subject, therefore, tends to have higher concentration of intravenously administered vectors. However, other organs such as heart would not have such advantage in systemic vector delivery, and would require a vector-targeting mechanism. Other vectors such as retroviral and lentiviral vector for example, have tissue tropism to lymphocytes, thus would require specific targeting mechanism to be delivered to other organ and non-dividing cells. Therefore, one could not extrapolate from the preferred embodiment in example 3 generally to conclude that gene targeting is not required for in vivo gene delivery to any cell by any route. Therefore, except for the intravenous administration of Ad-HO-I to

prepare for liver transplant and ex vivo perfusion with the Ad-HO-I, the specific example in the specification fails to support the full scope of the claims.

Thus, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. However, the specification only teaches using an adenoviral vector, and applicants solely rely on the submitted art as enablement support for the broad claims. Applicants are reminded that the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure** of any specific starting material **or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art**. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Apparently, the rule that a specification need not disclose that which is well known in the art simply means that omission of minor details does not cause a specification to fail the enablement requirement, and is not a substitute for an enabling disclosure. Failure to provide such teachings cannot be rectified by asserting that the

disclosure of the missing necessary information was well known in the prior art. See *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC, 1997).

Accordingly, for reasons of record and those set forth foregoing, the specification fails to meet the statutory enablement requirement for the claimed invention as they are broadly claimed.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
June 12, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER